BLOOD TREATMENT DEVICE

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This invention relates to the field of blood treatment devices having a blood purification element divided by a semipermeable membrane into two chambers, the first chamber being part of a dialysis fluid circuit and the second chamber being part of an extracorporeal blood circuit.

Such devices are used as hemodialysis machines in artificial kidney therapy. Through hemodialysis treatment, it is possible to withdraw excess water from a dialysis patient by means of a pressure gradient on a semipermeable membrane. On the other hand, substances such as urea and creatinine, which would otherwise be eliminated by healthy kidneys, are withdrawn from the patient according to a concentration gradient on the membrane. In the case of other substances - such as electrolytes - which are always present in blood in a certain concentration, concentrations corresponding to those in the blood of persons with healthy kidneys are usually used in the dialysis fluid.

Dialysis patients usually consume considerable quantities of potassium in their food intake between treatments. Excessive intake of potassium, in particular an accumulation over a long period of time due to inadequate elimination of potassium during dialysis, results in hyperkalemia (an elevated potassium concentration in the extracellular fluid).

The extracellular potassium concentration has an influence on the electrical resting membrane potential of cells. Therefore, this concentration influences the degree of electric stimulability of all stimulable cells (muscles, myocardium, nerves). The effect on cardiac electro-physiology in particular is important.

Abnormal values can lead to life-threatening arrhythmias. Therefore, the body regulates the potassium concentration within narrow limits. Under the pathophysiological conditions of renal failure, dialysis therapy must be conducted in such a way as to prevent critical states.

Normal potassium concentrations are in the range of 3.5- 4.5 mmol/L. Hyperkalemia is the condition when levels exceed 5.5 mmol/L; consequences include ventricular arrhythmia, ventricular fibrillations or even cardiac arrest. If the potassium level is below 2.5 mmol/L, this is called severe hypokalemia. Symptoms here include muscular weakness, atrial and ventricular arrhythmia, states of confusion and disorientation. The transitional ranges of mild hyperkalemia (4.5-5.5 mmol/L) and mild hypokalemia (2.5-3.5 mmol/L) are often largely symptom-free.

The potassium concentration is subject to much more complex kinetics during dialysis than the urea concentration, for example. Although urea is present in approximately the same concentrations intracellularly and extracellularly, the total potassium concentration of approximately 3500 mmol (50 mmol/kg) has a very irregular distribution: approx. 98 % is intracellular and only 2 % is extracellular. This imbalance between intracellular and extracellular concentrations is also influenced by changes in the concentration of other extracellular molecules, in particular H^+ ions, bicarbonate, glucose and insulin. Adrenergic stimulation and the aldosterone level also influence the concentration ratio. In addition, a strong rebound effect is observed, i.e., after the end of dialysis, the blood potassium concentration rises again considerably because of the time lag in the transfer from the intracellular space to the extracellular

space.

Removal of approximately 90 % of the quantity of potassium ingested since the previous treatment by intermittent dialysis is not always simple. Only a relatively low concentration gradient can be utilized. Initial potassium concentrations in dialysis patients are usually between approx. 3.6 and 7 mmol/L or in some cases even higher. The potassium concentration in the dialysis fluid is between 0 and 4 mmol/L, average concentrations of approx. 2 mmol/L being used in most cases. The usable gradients between blood and dialysis fluid therefore typically amount to 2-4 mmol/L at the start of dialysis, but are rapidly reduced during the treatment. Therefore, the total possible elimination of potassium is limited. If a larger quantity of potassium is ingested, there is also the risk that the total elimination may be too low. Therefore, patients are at risk of hyperkalemia, and this may be especially pronounced, in particular immediately before a dialysis treatment.

Using dialysis fluid having a low potassium concentration or even no potassium at all is not without risk. The potassium concentration may drop to a critically low level during dialysis, i.e., severe hypokalemia may be triggered (even if the total potassium level in the body is still adequate or even too high).

If the rate of potassium elimination is too high, it may lead to arrhythmia (J. P. Knochel: "Clinical Expression of Potassium Disturbances," in *The Regulation of Potassium Balance*, 1st edition, edited by D. W. Seldin, G. Giebisch, 1989, pp. 207-240; E. G. Lowrie and N. L. Lew: "Death Risk in Hemodialysis Patients: The Predictive Value of Commonly Measured

Variables and an Evaluation of Death Rate Differences Between Facilities," *American Journal of Kidney Disease* 15, pp. 458-482 (1990)). If there is an increase in the rate of elimination, the ratio of intracellular to extracellular potassium concentrations becomes greater, which then results in hyperpolarization of cells and thus a decline in stimulability. Therefore, there could be an increase in the probability of arrhythmia.

Administration of large quantities of bicarbonate to the patient, in particular in the early phase of dialysis, causes a shift in potassium from the extracellular space to the intracellular space, which also contributes to a reduction in the extracellular concentration and thus increases the risk of hypokalemia (in addition to the contribution made by the elimination of potassium via the dialysis machine).

There have been proposals for using model simulation with dialysis treatments to permit conclusions to be drawn regarding the removal of certain constituents of blood, in which case the calculations are supplemented by blood samples (S. Stiller, H. Mann and F. Raab, "Microprocessor-based universal dialysis calculator for individualization of artificial kidney dialysis," *MEDINFO '80*, edited by Lindberg/Kaihara, North-Holland Publishing Company, 1980, pp. 534-538).

U.S. Patent 4,244,787 describes a device in which the concentration of a substance in the blood inlet line can be determined by a sensor in the dialysis fluid outlet line. At the same time, it is possible to determine the total quantity of the substance removed.

U.S. Patent 4,508,622 describes a hemodialysis machine in which the electrolyte balance during a dialysis treatment can be determined by a sensor in the dialysis

fluid discharge line and a similar sensor in the dialysis fluid inlet line, and feedback to the dialysis treatment is made possible. A similar machine is disclosed in European Patent EP 0 330 892 A2.

The object of this invention is to improve upon a blood treatment device having a blood purification element which is divided by a semipermeable membrane into two chambers, the first chamber of which is part of a dialysis fluid circuit and the second of which is part of an extracorporeal blood circuit. The improvement is to consist of providing a better means of preventing nonphysiological states of the patient during the blood treatment.

This object is achieved with a blood treatment device having the features of Claim 1. Advantageous embodiments of this invention are the object of the subclaims.

According to this invention, the analyzer unit of the blood treatment device determines on the basis of at least one sensor in a blood circuit or dialysis fluid circuit the concentration of a substance, which can penetrate through the semipermeable membrane and is present in the blood in the blood inlet line; this is done in order to determine the concentration of a substance which can permeate through the semipermeable membrane and to determine the instantaneous transfer rate of the substance through the membrane as well as the total quantity of this substance removed during the treatment; to compare the concentration with a first admissible value range and compare the amount of the substance eliminated with a third value range; and the control unit which controls the blood treatment device can send instructions to the blood treatment device so that it performs the blood treatment while maintaining

all three admissible value ranges.

Such a device due to its inventive design allows critical substances such as potassium to be monitored and controlled within physiologically justifiable limits and periods of time during the blood treatment.

In an advantageous embodiment, the at least one sensor is situated in the dialysis fluid outlet line. If the concentration of the substance in question in the dialysis fluid inlet line is not known, another similar sensor may be provided there.

In the same way, it is also possible for such sensors to be provided in the blood circuit. However, because of the problems associated with contact with blood, sensors in the dialysis fluid circuit are generally preferable.

In a refinement of this invention, a target value within the third value range is stored in the analyzer unit, and the analyzer unit instructs the control unit so that the target value is reached at the end of the planned treatment period at the latest.

This invention can be used equally in a hemodialysis treatment or in a hemofiltration treatment. In the latter case, the dialysis fluid inlet line as the replacement fluid inlet line opens directly into the blood circuit, and the first chamber of the blood treatment machine is connected only to the dialysis fluid outlet line as the filtrate outlet line. Thus it is also possible in particular to use this machine in a combined treatment method, namely hemodiafiltration. For the sake of simplicity, however, the following discussion shall be devoted only to the components of a dialysis fluid circuit without interpreting this as

being restricted to hemodialysis.

Additional details and advantages of this invention are
described in greater detail below on the basis of an
exemplary embodiment which is shown schematically in
the drawing.

The blood treatment device shown in the single figure
has an extracorporeal blood circuit 10 and a dialysis
fluid circuit 20. In the blood circuit 10, blood is
taken from a patient (not shown) and sent through a
blood inlet line 11 to a second chamber 2 of a blood
treatment element 1, which is divided by a
semipermeable membrane 3 into two chambers 2 and 4.
From the second chamber 2, the blood goes back to the
patient through the blood return line 12. Blood is
circulated in the extracorporeal blood circuit 10 by a
blood pump 13.

In the dialysis fluid circuit 20, dialysis fluid goes
from a dialysis fluid processing unit 21 through the
dialysis fluid inlet line 22 to the first chamber 4 of
the blood treatment element 1. The dialysis fluid is
sent from the first chamber 4 through the dialysis
fluid outlet line 23 to an outlet 24. The dialysis
fluid is circulated here with the dialysis fluid pump
25.

The dialysis fluid processing unit 21 prepares the
dialysis fluid to be used according to specified mixing
ratios using water or water already mixed with a few
components of the dialysis fluid (connection 26) and a
potassium concentrate 27 or to potassium concentrates
27 and 28 through concentrate pumps 29 and 30. It is
possible to rely on proven components with which those
skilled in the art are familiar but which need not be
specified in detail here. Within the scope of this

invention, it is essential only that the addition of the potassium concentrate to the dialysis fluid processing unit 21 can be adjusted in accordance with setpoint values.

A particularly advantageous implementation for providing dialysis fluid with an upper and a lower limit to the potassium concentration consists of working with two concentrates 27 and 28, whereby the first concentrate 27 has a low potassium concentration and the second concentrate 28 has a higher potassium concentration. If these concentrates also contain other substances, for example, the acidic components of the dialysis fluid and other electrolytes, then they are expediently present in both concentrates in equal concentration. Then at a constant rate of addition which is the sum of the concentrate flow pumped by the concentrate pumps 29 and 30, the potassium concentration can never go beyond a certain concentration range in the dialysis fluid.

A potassium-sensitive sensor 31 is provided in the dialysis fluid outlet line 23 and is connected by a line 31' to an analyzer unit 32. The analyzer unit 32 is in turn connected by a data line 33 to a control unit 34. The analyzer unit 32 and the control unit 34 may be designed as a single integrated unit. The control unit 34 is connected to the actuators and sensors of the blood treatment device to be able to perform the blood treatment as such in a controlled manner. To explain the present invention, these actuators and sensors include in particular the concentrate pumps 29 and 30 on the dialysis fluid pump 25 as well as the blood pump 13 which are connected by appropriate control lines 13', 25', 29' and 30' to the control line.

For the design of other components such as thermostatic units, monitoring units and balancing units, which are conventional in such a blood treatment machine, a variety of embodiments are known to those skilled in the art and therefore will not be discussed in greater detail here.

Now according to this invention, three admissible value ranges are stored in the analyzer unit 32 for the concentration CBI of potassium in the blood inlet line 11, for the transfer rate $\Delta M/\Delta t$ of potassium through the semipermeable membrane 3 and the total quantity M withdrawn.

For the first range, the minimum limit is preferably 2.5-3.5 mmol/L and the maximum limit is 4.5-5.5 mmol/L. It is also possible to provide a narrower first value range and an additional first value range which includes the former so that a milder form of hyperkalemia and hypokalemia and a more severe form of each can be counteracted in the form of two alarm levels.

For the second admissible value range, expediently a lower limit of 0 mmol/min is set because in general potassium is to be withdrawn from the patient. However, it is also possible to select a negative lower limit if it is suspected that the patient is already hypokalemic at the beginning of the treatment.

In the case of the third admissible value range, first a target value Mend for the total quantity of potassium to be withdrawn is stored in the analyzer unit 32. This target value can be input by an operating person via an interface (not shown in detail) or it may be set by the analyzer unit itself on the basis of reference data. In the simplest case, the third admissible value range is

simply defined by a lower limit of 0 mol and by the upper limit Mend – i.e., the same as the target value.

The following processes take place in the blood treatment machine during the blood treatment.

The dialysis treatment is begun with a conventional composition of the dialysis fluid and conventional values for the blood flow Qb and the dialysis fluid flow Qd. After a measurement phase of a few minutes, at which point stable measured values have been established, the analyzer unit 32 obtains from the sensor 31 the concentration value Cdo of potassium in the dialysis fluid outlet line 25. In addition, the concentration Cdi of potassium in the dialysis fluid inlet line 22 is known to the analyzer unit 32 due to the predefined values of the control unit 34. To this end, a second similar sensor may also be provided in the dialysis fluid inlet line 22. The analyzer unit 32 determines with this information the blood concentration Cbi of potassium in the blood inlet line 11 using the following equation (J. A. Sargent and F. A. Gotch: "Principles and biophysics," in: *Replacement of Renal Function by Dialysis*, edited by C. Jacobs, et al., Kluwer Academic Publishers, Dordrecht, 1996, pp. 34ff):

$$Cbi = \frac{Qd(Cdo - Cdi)}{\alpha D} + \frac{Cdi}{\alpha} \tag{1}.$$

where D is the dialysance and ∀ is the Gibbs-Donnan coefficient for potassium. The Gibbs-Donnan coefficient takes into account the ionic character of potassium for the transport properties through a semipermeable membrane, where $\alpha = 1$ can be equated in first

approximation. Otherwise another value determined accordingly is stored in the analyzer unit 32.

The dialysance D may have been previously entered into the analyzer unit by the user or it may have been measured initially by the blood treatment device using the known methods for this purpose. For example, the technique described in U.S. Patent 5,100,554 may be used for this purpose. It is not necessary to determine the dialysance for potassium directly. It is sufficient to determine the dialysance for some other substance which has a fixed relationship to the dialysance for potassium, as is the subject of German Patent Application 10317024.3, to the disclosure content of which reference is herewith made explicitly.

Other methods, such as the method described in U.S. Patent 6,126,831, for example, may also be used for the determination of Cbi.

For the sake of simplicity, the ultrafiltrate flow Qf, i.e., the net flow rate through the semipermeable membrane 3 from the second chamber 2 to the first chamber 4 has been equated with zero in equation (1). Those skilled in the art will be aware of modified equations, which take into account an ultrafiltration rate Qf that is not negligible. In this connection, reference is made explicitly to German Patent Application 10212247.4 by the present applicant for the application of this formalism to hemofiltration and hemodiafiltration.

After a brief initial measurement phase, the analyzer unit 32 compares the initial measured value of Cbi with the first admissible value range stored [in the unit]. If the value is already outside the admissible value range, the analyzer unit 32 delivers an alarm signal

via the control unit 34 and draws attention to the
critical blood concentration via a display and input
unit 35, which is connected to the control unit over a
data line 36. The blood treatment is stopped
automatically, so that the operating personnel can
perform the additional steps.

If the measured value is within the first admissible
range, the analyzer unit specifies, on the basis of the
limits of the first and second admissible ranges and
optionally the third admissible range, the additional
treatment parameters so that the target value Mend for
the total quantity of potassium to be withdrawn can be
achieved as rapidly as possible within the third
admissible value range without leaving all of the
admissible value ranges. To do so, the dialysis fluid
concentration is set at a value which is close to the
lower limit of the first value range or at least at a
distance from the instantaneous concentration value
through a minimum difference. The dialysis fluid flow
Qd or the blood flow Qb may optionally also be
increased. In this way the dialysance and thus the
transfer rate $\Delta M/\Delta t$ are also increased. The analyzer
unit here may either proceed empirically or it may
estimate the amount of time required for withdrawal of
the quantity Mend on the basis of known equations for
the dialysance of the concentrations and flows – as
discovered in German Patent Application 10212247.4 so
that it is possible to propose treatment parameters
which permit complete withdrawal [of the substance]
within the total treatment time T.

After this initial phase, the actual blood treatment
begins. At regular intervals, the sensor 31 relays
measured values to the analyzer unit 32 which
determines the blood concentration Cbi(t) as described
above and then also determines the transfer rate

$\Delta M(t)/\Delta t$ and the total quantity of potassium withdrawn $M(t)$ with the help of equations (2) and (3):

$$\frac{\Delta M(t)}{\Delta t} = Qd(t) \cdot (Cdo(t) - Cdi(t)) \qquad (2).$$

$$M(t) = \int_0^t Qd(t') \cdot (Cdo(t') - Cdi(t')) \cdot dt' \qquad (3).$$

The analyzer unit 32 compares all three values with the respective admissible value ranges. If there is the risk that the value will depart from the first or second range, then the analyzer unit 32 gives the control unit 34 appropriate instructions so that it is possible to counteract the tendency to leave the value ranges. For example, if the value for $Cbi(t)$ is dropping too rapidly, the concentration of $Cdi(t)$ can be increased accordingly. It is also possible to reduce the blood flow $Qb(t)$ or the dialysis fluid flow $Qd(t)$. The same thing is also true if the transfer rate $\Delta M(t)/\Delta t$ is too high.

On reaching the target value $Mend=M(t)$, but at the latest on reaching the upper limit of the third value range – if these values differ from one another for some reason, the control unit 34 is instructed to set the potassium concentration $Cdi(t)$ at a value corresponding to the blood value $Cbi(t)$ so that by the end of the blood treatment there is no further withdrawal of potassium.

If the treatment time T has elapsed without being able to achieve the target quantity Mend despite the maximum transfer rate, this information is displayed to the user accordingly. To do so, the information may already be displayed for the user on entry of the treatment data because the maximum quantity of a substance to be

removed during the treatment time T is obtained from the upper limit for the transfer rate multiplied by the treatment time T.

All the values calculated in the meantime are displayed for the operating person via the display and input unit 35. A wide variety of graphic aids may be used to display the individual values in relation to the admissible value ranges and any imminent departure of the value from the value ranges in a comprehensible manner. It is particularly advantageous to have an updated display directly after the initial determination of the potassium concentration because this value permits conclusions to be drawn regarding the tolerability of the treatment and a possible individualized adjustment of the individual value ranges. The analyzer unit 32 may also make recommendations regarding the individual value ranges on the basis of stored relationships with other patient-specific data such as height and weight.

The design of the blood treatment unit according to this invention prevents the blood concentration and the transfer rates of a substance passing through the semipermeable membrane of a blood treatment machine from going beyond physiological ranges, while at the same time a treatment in the sense of a quantity of a substance to be withdrawn is made possible with prioritized observance of the limits for the blood concentration and the transfer rate.